IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	Smith et al.
Appl. No.:	10/634,663
Conf. No.:	6356
Filed:	August 5, 2003
Title:	IN VITRO CELL CULTURE EMPLOYING A FIBRIN NETWORK IN A FLEXIBLE GAS PERMEABLE CONTAINER
Art Unit:	1797
Examiner:	Nathan Andrew Bowers
Docket No.:	WM-5934 (R1) US (112713-983)

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APPELLANTS' REPLY BRIEF

Sir:

I. INTRODUCTION

Appellants submit this Reply Brief in response to the Examiner's Answer dated November 25, 2008 pursuant to 37 C.F.R. § 41.41(a). Appellants respectfully submit that the Examiner's Answer has failed to remedy the deficiencies with respect to the Final Office Action dated June 5, 2008 as noted in Appellants' Appeal Brief filed on October 8, 2008 for at least the reasons set forth below. Accordingly, Appellants respectfully request that the obviousness rejections of pending Claims 1, 3-11, 19-21 and 23-53 be reversed.

II. THE EXAMINER HAS STILL FAILED TO SHOW THAT INDEPENDENT CLAIMS 1, 48 AND 51 ARE RENDERED OBVIOUS BY *SMITH, TONER, TURNER* AND *CODNER*

Appellants respectfully request that the Board reverse the 35 U.S.C. §103 rejection because the Examiner has still failed to demonstrate that *Smith*, *Toner*, *Turner* and *Codner* disclose or suggest every element of independent Claims 1, 48 and 51. Independent Claims 1, 48 and 51 recite, in part, a closed supporting container comprising a side wall having a flexible interior surface comprising an ethylene vinyl acetate (EVA) copolymer. A fibrin matrix layer is on a portion of the EVA copolymer interior surface of the side wall of the supporting container.

The present claims provide an in vitro cell culture employing a fibrin network in a flexible container. Appellants have surprisingly found that providing the flexible container with an interior surface of a portion of the side walls constructed from an EVA copolymer having a fibrin matrix presents an environment conducive to adherent cell proliferation and maturation. By incorporating a fibrin matrix in a flexible cell culture container, the fibrin matrix lessens the functional biocompatibility requirements of the materials from which the container is fabricated. By transferring the biocompatibility requirement of the culture from the container to the fibrin matrix, the material selection of the container can focus on other attributes, such as gas permeability, optical clarity, and material strength. Accordingly, the flexible container having an interior surface comprising an EVA copolymer and a fibrin matrix layer on a portion of the interior surface is well suited for applications involving therapeutic transplantation of cultured cells.

Even if combined, *Smith*, *Toner* and *Turner* fail to disclose or suggest a flexible interior surface comprising an EVA copolymer as required by Claims 1, 48 and 51. *Smith*, *Toner*, *Turner* and *Codner* also fail to disclose or suggest a fibrin matrix layer on a portion of the EVA copolymer interior surface as required by Claims 1, 48 and 51.

In the Examiner's Answer, the Examiner admits that the EVA copolymer layer of *Smith's* container does not represent the inner cell growth surface. See Examiner's Answer, page 12-13. Rather, the interior cell growth surface of *Smith's* container is a polystyrene layer. The Examiner then asserts that, because *Toner* and *Turner* teach that fibrin is known in the art as an effective material to facilitate cell immobilization, the skilled artisan would have found it

obvious to replace the polystyrene layer of *Smith* with a fibrin layer. Once the polystyrene layer is removed from *Smith's* container, the Examiner alleges, the pre-existing EVA layer would become the inner layer and be coated by fibrin.

Appellants respectfully disagree with the Examiner's assertion and submit that the skilled artisan would have no reason to replace the polystyrene layer of *Smith's* container with a fibrin layer taught by *Toner* or *Turner*. For example, *Smith* explicitly teaches away from an interior surface comprising an EVA by stating:

> While EVA [ethylene vinyl acetate] can hold an electrostatic charge, the charge has the undesirable tendency to decay over time. Eventually, the decay of the charge on EVA will render the container ineffective for growing adherent cells. Rigid styrene flasks with an electrostatic charge are known, and show less of a tendency to lose charge over time.
> See *Smith*, column 2, lines 7-12 (emphasis added).

Accordingly, *Smith* would lead the skilled artisan away from using any ethylene vinyl acetate copolymer for an interior cell growth surface of a cell culture container in accordance with the present claims.

The Examiner further asserts that fibrin and polystyrene are both effective in accommodating the immobilization of adherent cells, and therefore are considered functionally equivalent and interchangeable. See Examiner's Answer, page 12-13 and 15. Appellants respectfully disagree. For example, a polystyrene layer is a completely solid/gas impermeable material throughout (e.g. polystyrene is known in the art as a rigid, gas-impermeable plastic), and adherent cells can only grow on the surface of the polystyrene layer.

On the other hand, a fibrin matrix has specific conformations and three dimensional characteristics that can create a framework for the culture of cells, tissues and perhaps portions of organs. The cells adhere to and embed in the fibrin matrix, so that the spatial characteristics of the matrix can be conferred upon the tissue growing thereon. Adherent cells do not embed within the polystyrene layer because they are unlikely to permeate the polystyrene layer in the same manner as they would in a fibrin matrix. As a result, skilled artisan would understand that the polystyrene layer and fibrin matrix operate in different manners and are not functionally equivalent.

References must be considered as a whole and those portions teaching against or away from each other and/or the claimed invention must be considered. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve Inc.*, 796 F.2d 443 (Fed. Cir. 1986). "A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Applicant." *Monarch Knitting Machinery Corp. v. Fukuhara Industrial Trading Co., Ltd.*, 139 F.3d 1009 (Fed. Cir. 1998), quoting, *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994). Because *Smith* explicitly teaches away from using EVA as a surface for growing adherent cells and because polystyrene layers and fibrin matrixes are functionally different for growing adherent cells, the skilled artisan would have no reason to replace the polystyrene layer of *Smith* with a fibrin layer of *Toner* or *Turner* in the absence of hindsight.

Toner is further relied upon by the Examiner for the teaching that a fibrin matrix may be used to accommodate cell growth. In the Examiner's Answer, the Examiner alleges that *Toner* teaches the skilled artisan that fibrin is not only biocompatible, but also readily combinable with an EVA base layer. See Examiner's Answer, pages 12-13.

Appellants respectfully disagree and submit that *Toner* fails to teach or even suggest a fibrin matrix layer on a portion of the ethylene vinyl acetate copolymer interior surface or that fibrin is readily combinable with an EVA layer in accordance with the present claims. *Toner* teaches a polymeric membrane 30 that separates a liquid compartment and an oxygenated fluid compartment of the cartridge. *Toner* discloses the term "fibrin" in a single instance as one of many coating materials that can be applied to the polymeric membrane 30. See *Toner*, column 11, lines 48-55.

In addition, the only time *Toner* mentions the use of an EVA layer for the polymeric membrane 30 is as the middle layer of a three-layered co-extruded film of styrene-butadiene-styrene/ethyl vinyl acetate/styrene-butadiene-styrene (SBS/EVA/SBS). See *Toner*, column 9, lines 39-42. The applied fibrin coating would then contact only one of the outer SBS layers. As a result, the EVA middle layer of the membrane does not directly contact any fibrin. *Toner* provides no example of monolayer EVA film. Consequently, *Toner* provides no examples or specific teaching to the skilled artisan that fibrin is readily combinable or compatible with an EVA layer.

Turner fails to disclose or suggest the use of an ethylene vinyl acetate copolymer anywhere in his disclosure. *Codner* fails to disclose or suggest the use of fibrin for growing cells anywhere in his disclosure. As a result, *Turner* and *Codner* fail to teach or suggest to the skilled artisan utilizing a fibrin matrix layer on a portion of an ethylene vinyl acetate copolymer interior surface in accordance with the present claims.

In sum, the cited references fail to disclose or suggest every element of independent Claims 1, 48 and 51. Appellants respectfully submit that the Examiner is using Appellants' patent application as a road map for creating hindsight obviousness and has failed to set forth sufficient reasons for how the skilled artisan would have arrived at the claimed invention in view of *Smith*, *Toner*, *Turner* and *Codner*. Moreover, the cited references fail to even recognize the advantages, benefits and/or properties of a fibrin matrix layer on a portion of an interior surface composed of an ethylene vinyl acetate copolymer in accordance with the present claims and provide no reasonable expectation of success with respect to same. Accordingly, Appellants respectfully submit that independent Claims 1, 48 and 51, along with Claims 3-11, 19-21, 23-47, 49-50 and 52-53 that depend from Claims 1, 48 and 51, are novel, nonobvious and distinguishable from the cited references and are in condition for allowance.

III. THE EXAMINER HAS STILL FAILED TO ESTABLISHED A *PRIMA FACIE* CASE OF OBVIOUSNESS WITH RESPECT TO CLAIMS 36-46

Claims 36-46 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Smith*, *Toner*, *Turner, Codner* and *Delmotte*. Appellants respectfully submit that the patentability of Claim 1 over *Smith*, *Toner*, *Turner* and *Codner* as discussed above also demonstrates that the obviousness rejection of Claims 36-46, which depend from Claim 1, is improper. In this regard, even with *Delmotte* as a reference, the cited art fails to teach or suggest the elements of Claims 36-46 in combination with the novel elements of Claim 1.

The Examiner asserts that *Delmotte* is used as evidence that it is known in the art to form a fibrin matrix by delivering a first solution of fibrinogen and factor XIII and a second solution of thrombin and calcium to a desired surface. See Examiner's Answer, page 16. Nevertheless, along with *Smith*, *Toner*, *Turner* and *Codner*, *Delmotte* fails to disclose or suggest a fibrin matrix

layer on a portion of the ethylene vinyl acetate copolymer interior surface as required by Claim 1. Instead, *Delmotte* is directed to rigid syringes that are used as a medical delivery device. *Delmotte* fails to even disclose or suggest the use of ethylene vinyl acetate copolymer anywhere in his disclosure.

In addition, *Delmotte* teaches away from a closed support container having flexible and gas permeable exterior sidewalls in accordance with the present claims. As a result, teachings directed to *Delmotte's* rigid, impermeable syringes would lead the skilled artisan away from the flexible, permeable container of *Smith*.

In sum, even when combined, *Smith*, *Toner*, *Turner*, *Codner* and *Delmotte* fail to disclose or suggest every element of independent Claim 1. Accordingly, Appellants respectfully submit that independent Claim 1, along with Claims 36-46 that depend from Claim 1, are distinguishable from the cited references and are in condition for allowance.

IV. CONCLUSION

For the foregoing reasons, Appellants respectfully submit that the Examiner's Answer does not remedy the deficiencies noted in Appellants' Appeal Brief with respect to the Final Office Action. Therefore, Appellants respectfully request that the Board of Appeals reverse the obviousness rejections with respect to Claims 1, 3-11, 19-21 and 23-53.

No fee is due in connection with this Reply Brief. The Director is authorized to charge any fees that may be required, or to credit any overpayment to Deposit Account No. 02-1818. If such a withdrawal is made, please indicate the Attorney Docket No. 112713-983 on the account statement.

Respectfully submitted,

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